bezlotoxumab (Zinplava™)

Policy # 00560
Original Effective Date: 05/17/2017
Current Effective Date: 05/16/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider bezlotoxumab (Zinplava™)‡ to reduce the recurrence of Clostridium difficile infection to be **eligible for coverage.**

Patient Selection Criteria
Coverage eligibility for bezlotoxumab (Zinplava) will be considered when the following criteria are met:

- Patient currently has a diagnosis of Clostridium difficile infection as confirmed by appropriate testing; AND
- Patient is 18 years of age or older; AND
- Patient has NOT previously received Zinplava for the current Clostridium difficile infection; AND
- Zinplava is dosed at 10 mg/kg as a one-time dose; AND
- Patient will receive standard of care antibiotics for the treatment of Clostridium difficile infection in conjunction with Zinplava; AND
- Patient is at high risk for Clostridium difficile infection recurrence, which is evidenced by a prior history of Clostridium difficile infection within the past 6 months AND at least ONE of the following:
    - Patient is 65 years of age or older; OR
    - Patient has severe Clostridium difficile infection as evidenced by a ZAR score of greater than or equal to 2; OR
    - Patient is immunocompromised (e.g. active hematological malignancy, current use of an antineoplastic or immunomodulating agent, current use of chronic corticosteroids, asplenia, current neutropenia or pancytopenia, prior solid organ transplant, having AIDS or other immunodeficient condition)

Note: The ZAR score is calculated as follows:

- *Age >60 (1 point)*
- *Body temperature >100 degrees Farenheit (1 point)*
- *Albumin level <2.5 mg/dL (1 point)*
- *Peripheral WBC >15,000 cells/mm3 within 48 hours (1 point)*
- *Endoscopic evidence of pseudomembranous colitis (2 points)*
- *Treatment in ICU (2 points)*

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When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of bezlotoxumab (Zinplava) when the patient selection criteria are not met to be **investigational.***

Background/Overview

Zinplava is a human monoclonal antibody that binds to Clostridium difficile toxin B, and is indicated to reduce the recurrence of Clostridium difficile infection in patients 18 years of age or older who are receiving antibacterial drug treatment of Clostridium difficile infection and are at high risk for Clostridium difficile infection recurrence. Zinplava is not indicated for the treatment of Clostridium difficile infection. Zinplava is not an antibacterial drug, and it should only be used in conjunction with antibacterial drug treatment of Clostridium difficile infection. The recommended dose of Zinplava is 10 mg/kg administered one time as an intravenous infusion over 60 minutes.

Clostridium difficile Infection
Clostridium difficile is an anaerobic gram positive, spore forming, toxin-producing bacillus that is transmitted through the oral-fecal route. This pathogen is commonly found in healthcare facilities. Typically, colonization is prevented by the barrier properties of fecal microbiota, however disruption of the normal gastrointestinal flora by antibiotics in the major cause of Clostridium difficile infection. Currently, two oral antibiotics are FDA approved for the treatment of Clostridium difficile infection [Dificid®‡ (fidaxomicin) and vancomycin]. Metronidazole is also commonly used for the treatment of Clostridium difficile infection even though it is not technically FDA approved for the indication. Zinplava is the first drug FDA approved to reduce the recurrence of Clostridium difficile infection.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Zinplava is a human monoclonal antibody that binds to Clostridium difficile toxin B, and is indicated to reduce the recurrence of Clostridium difficile infection in patients 18 years of age or older who are receiving antibacterial drug treatment of Clostridium difficile infection and are at high risk for Clostridium difficile infection recurrence.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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Zinplava was evaluated in two randomized, double-blind, placebo controlled trials in patients receiving standard of care antibiotics for the treatment of Clostridium difficile infection. In the first trial, adults with a primary or recurrent Clostridium difficile infection receiving standard of care antibiotics along with Zinplava demonstrated a lower recurrence of Clostridium difficile infection vs. those on standard of care antibiotics plus placebo (17% vs. 28%, respectively, p<0.001). In the second trial, similar results were reported. The recurrence of Clostridium difficile infection was lower in the Zinplava group compared to the placebo group (16% vs. 26%, p<0.001).

A post hoc analysis (based on data on file at Merck) of Clostridium difficile infection recurrence in subgroups with a history of at least one Clostridium difficile infection episode in the previous 6 months and at least one additional risk factor [≥65 years of age, severe Clostridium difficile infection (via a ZAR score or at least 2), or an immunocompromised patient) demonstrated that the use of Zinplava resulted in absolute risk reduction rates of at least 20% (versus lower absolute reduction rates reported in the trials mentioned above). It should be noted that this post hoc analysis was not powered to show significance, however these results provide guidance in narrowing the use of this drug to those who would most likely benefit from its effects due to the absence of a standard definition of "high risk for Clostridium difficile infection recurrence."

References

1. Zinplava [package insert]. Merck and Company, Incorporated. Whitehouse Station, New Jersey. Updated October 2016.
2. Medical Information Response via Merck. March 24, 2017.
3. Zinplava Drug Evaluation. Express Scripts. Updated January 2017.

Policy History

Original Effective Date:	05/17/2017
Current Effective Date:	05/16/2018
05/04/2017	Medical Policy Committee review
05/17/2017	Medical Policy Implementation Committee approval. New Policy.
05/03/2018	Medical Policy Committee review
05/16/2018	Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date:	05/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense

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medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J3490 Code added eff 1/1/18: J0565
ICD-10 Diagnosis	A04.7

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association TEC or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.